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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/306,662	05/05/1999	MARK K. MALMROS	PRO-SE	3760

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/306,662	MALMROS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7-11 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7-11 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed February 5, 2004 is acknowledged and has been entered. Claims 1 and 10 have been amended. Claim 20 has been added.

2. Claims 1, 5, 7-11, and 20 are pending in the application and are currently under prosecution.

Response to Applicant's Remarks

3. At page 2 of the amendment filed February 5, 2004, Applicant has remarked: "Claim 12 is added". Actually, claim 20 has been newly added by the amendment; and claim 12 had been previously canceled.

Furthermore, at page 2 of the amendment, Applicant has addressed the status of the application following the mailing of the previous Office action. Applicant is directed to the interview summary mailed January 8, 2004, which clarified the status of the application following the mailing of said Office action.

Grounds of Claim Rejections Withdrawn

4. Applicant's amendment of February 5, 2004 to claim 10 has obviated a ground of rejection under 35 USC § 112, second paragraph, which was set forth in section 10 of the previous Office action mailed December 18, 2002.

Claim Objections

5. Claim 1 is objected to because of the typographical error in line 3, namely "fromt eh".

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 5, 7-11, and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reason set forth in section 9 of the previous Office action mailed December 18, 2002.

At pages 5 and 6 of the amendment filed August 27, 2003, Applicant has asserted written support for the terms "the degree of the metachromatic shift of the dye from the reflected light spectrum of the stained tissue or cells" and "the degree of the metachromatic shift of the dye from a library" may be found in the originally filed specification at, for example, page 8, lines 9-16, and page 22, lines 1-5. Accordingly, Applicant has argued this ground of rejection should be withdrawn.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

The disclosure at page 8, lines 9-16, reads:

> The histochemical pathology of dysplastic, pre-cancerous, and cancerous lesions that would be expected to be stained with any of the thiazine dyes will vary as to the degree of metachromasia within the cell tissue layer.

The disclosure at page 22, lines 1-5, reads:

> For example, the software analysis of the spectra may compare the metachromatic shift of the stain toluidine blue O between two or more specific wavelengths by correlation. The results are then compared to a body of data previously collected and correlated to underlying conventional histochemical data defining the cellular stage of metaplasia.

Accordingly, the disclosure at page 8 to which Applicant has referred appears to suggest that the degree of metachromasia varies within the "cell tissue layer", such that the "histochemical pathology" of such lesions will vary, while the disclosure at page 22 to which Applicant has referred suggests software can be used to compare the metachromatic shift of the dye at two or more specific wavelengths. In contrast, claim 1

recites: "A method for diagnosing dysplasia, pre-cancer or cancer in situ in biological tissue or cells of a living organism, comprising: [...] comparing the degree of the metachromatic shift of the dye from the reflected light spectrum of the stained tissue or cells with the degree of the metachromatic shift of the dye from a library of previously obtained spectra of similarly stained tissue or cells". The disclosure at page 8 does not suggest comparing the degrees of the metachromatic shifts of the reflected light spectrum of a dye measured and recorded using a stained tissue or stained cells and a library of previously obtained spectra of similarly stained tissue or similarly stained cells. The disclosure of page 22 does not refer to measuring and recording the degree of a metachromatic shift in the reflected light spectra of either a stained tissue or stained cells and a library of previously obtained spectra of similarly stained tissue or similarly stained cells. Accordingly, the disclosures to which Applicant has referred do not appear to provide the necessary written support for the claim language.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 5, 7-11, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reason set forth in sections 7 and 10 of the previous Office action mailed December 18, 2002.

At pages 2-5 of the amendment filed August 27, 2003, Applicant has traversed these grounds of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

At page 3, paragraph 2, Applicant has argued one skilled in the art would know how to quantitate the metachromasia by measuring the extent of the metachromatic shift by comparing the intensity of light in a desired light spectrum between, for example, two or more specific wavelengths. However, the previous Office action stated the claims are vague and indefinite because the terms "the metachromatic shift" and

"the degree of the metachromatic shift" appear not to be defined in the specification, so it cannot be determined how the spectra are to be compared, or more precisely what aspect or characteristic of the spectrum are to be compared with the library of previously obtained spectra. Applicant has argued the artisan would know how to quantitate the metachromasia; the question however is not whether the artisan would know how, but whether the artisan could determine the metes and bounds of the subject matter that Applicant regards as the claimed invention. Because it cannot be determined how the spectra are to be compared, or more precisely what aspect or characteristic of the spectrum are to be compared with the library of previously obtained spectra, since the terms "the metachromatic shift" and "the degree of the metachromatic shift" appear not to be defined in the specification are defined, the artisan cannot know or determine those metes and bounds.

At page 3, paragraphs 3 and 4, Applicant has argued the phrase "with a library of previously obtained spectra of similarly stained tissue or cells" would be clear to the skilled artisan, since upon reviewing the disclosure, the artisan would be aware that the library of previously obtained spectra would include those cells and/or tissues that are the subject of the particular analysis and are obtained from individuals that may exhibit the particular cellular abnormality, e.g., skin cancer. In reply, the previous Office action stated the recitation of the phrase renders the claim vague and indefinite because it cannot be determined from which similarly stained tissue or cells said library of previously obtained spectra is to be obtained prior to steps (a)-(d) and from what source said similarly stained tissue and cells are to be derived. Now, Applicant has argued the similarly stained tissue or cells **may** exhibit the particular cellular abnormality. Even if the specification discloses by example that the tissues or cells, which have been similarly stained, and from which the library of spectra is generated, are tissues and cells obtained from individuals that may exhibit the particular cellular abnormality, while limitations are not read into the claims, such a disclosure would not be limiting, as it would be merely exemplary. Accordingly, it still it cannot be determined from which similarly stained tissue or cells said library of previously obtained spectra is to be obtained or from what source said similarly stained tissue and cells are to be derived in

practicing Applicant's invention. Accordingly, the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter that Applicant regards as the invention.

Regarding the recitation of "correlating the reflected light spectrum with a disease state", at page 4, paragraphs 2 and 3, Applicant has argued the pending claims are sufficiently definite, because at page 22, lines 1-5, the specification explains one can compare the extent of metachromatic shift in the test sample spectra with that obtained from the library of previously obtained spectra of similarly stained tissue or cells, which have been previously diagnosed by conventional techniques, to determine the disease state of the test sample. However, the previous Office action stated, it cannot be ascertained how correlating the reflected light spectrum with a disease state leads to a diagnosis of a dysplasia, pre-cancer, or cancer in a living organism, since it cannot be determined how the spectrum of reflected light and disease state are related. The previous Office action further queried, Is the relationship true of every type of spectrum of reflected light generated by either methylene blue or toluidine blue O, and of every type of disease state? Although Applicant has amended claim 1 to recite the disease state is selected from the group consisting of dysplasia, pre-cancer, and cancer, it is nonetheless unclear how the method is to be used to meet the objective recited in the preamble of the claim, because it cannot be determined how the claim requires the reflected light spectrum be correlated with such a disease state. Contrary to Applicant's assertions, for reasons already addressed above, the specification does not appear to guide one to compare the extent of metachromatic shift in the test sample spectra with that obtained from the library of previously obtained spectra of similarly stained tissue or cells, which have been previously diagnosed by conventional techniques. Moreover, the claims do not expressly recite correlating the extent of metachromatic shift and disease state; rather the claims recite correlating the reflected light spectra and disease state. In addition, even if the specification discloses by example that the library of spectra can be generated by an analysis of similarly stained tissue or cells from individuals that may exhibit the particular cellular abnormality, again, such a disclosure would not be limiting, as it would be merely exemplary.

At page 5, paragraph 2, Applicant has argued that with reference to the term "similarly stained", the skilled artisan would be aware the tissue or cells should be stained according to the same protocol. However, the claims merely recite the tissue or cells be similarly stained. Thus, the metes and bounds of the subject matter that Applicant regards as the invention is not particularly or distinctly claimed, since it cannot be ascertained how similarly the different tissue or cells must be stained.

Claim Rejections – 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1, 5, 7-11, and 20 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by US Patent No. 5,784,162-A, as evidenced by Vaezy et al. *(Journal of Microscopy* **163**: 85-94, 1991) and Marchesini et al. *(Photochemistry and Photobiology* **55**: 515-522, 1992), for the reason set forth in section 13 of the previous Office action mailed December 18, 2002.

By the amendment filed August 27, 2003, Applicants have traversed the ground of this rejection, in part, reiterating the arguments set forth previously and, in part, adding new arguments.

Applicants' arguments have been carefully considered but have not been found persuasive. A more thorough review of Applicant's previous arguments and the Examiner's rebuttal of record can be found in Office Action mailed December 18, 2002.

Briefly addressing Applicant's reiterated arguments, contrary to Applicant's assertion, the prior art teaches methods for diagnosing cancer, as is evident upon consideration of the disclosures throughout the document. While the disclosed methodology finds broader application in the art, the prior art expressly teaches methods by which the ordinarily skilled artisan can diagnose cancer, which methods involve *in situ* measurements and quantification of the spectral shifts of stained tissue or cells of a present subject and comparison of the measured and quantified spectral shifts to those of a library of spectral shifts acquired from similarly stained samples of tissue or cells, which were acquired from previously diagnosed subjects, such that a determination can be made of whether or not the tissue or cells of the present subject are cancerous.

In reply to Applicant's argument that the skilled artisan would not recognize that metachromasia could be used in diagnosing cancer, at the time of the disclosure by the prior art, as evident by Applicant's own disclosure, it had long been appreciated in the art that thiazine dyes, such as methylene blue and toluidine blue, display metachromasia; i.e., they stain certain cell components a different color than the original color of the dye. At page 5 of Applicant's disclosure, for example, Applicant discloses Canto et al. used methylene blue to selectively stain metaplastic cells *in situ*, so as to distinguish metaplastic cells in the esophagus from normal cells by visually examining the contrasting coloration of the metaplastic cells and the normal cells.

Therefore, as noted previously, "metachromasia" is no more than a fanciful way of describing the change in the absorption or transmission spectrum of a dye that occurs after staining two different types of tissue or cells. The "metachromatic shift of the dye" to which the claims refer, thus, is interpreted to denote the change that is observed in the transmission spectrum of a dye after staining a particular tissue or cell relative to that which was previously observed after staining another tissue or cell, or relative to a composite of transmission spectra observed after staining a library of tissues or cells. The change in the absorption or transmission spectra of a dye, or the metachromatic shift is an inherent property of the dye.

Therefore, again in response to Applicant's argument that the prior art does not teach or suggest quantifying the metachromatic shift of a dye and correlating the presence of a shift with the presence of cancerous cells or tissue, to the contrary, there is no manipulative difference between the steps practiced in performing the claimed invention and those practiced in performing the prior art's disclosed methods for diagnosing cancer. The methods of the prior art differentiate cancerous tissue and normal tissue on the basis of differences or similarities that are observed in the transmission spectra of a dye after staining a sample containing suspected cancerous cells and a library of tissues or cells that have been previously characterized as either cancerous or not. Therefore, in practicing the method of the prior art, the artisan necessarily determined the metachromatic shift of the dye that was used to stain the tissues or cells.

Having carefully considered the whole of Applicant's arguments, it is apparent that Applicant has ignored the actual invention that is disclosed and claimed by the prior art. Although Applicant has repeatedly argued the prior art only teaches the use of the dyes, e.g., methylene blue, as "contrast agents", the term "contrast agent" has traditionally been applied to an agent, such as a dye, that enables the artisan to *visually* differentiate between two different types of cell or tissue on the basis of the *contrasting* coloration or staining of those cells or tissues by the dye. The prior art's methods for diagnosing cancer comprise measuring and recording the spectral shifts, so that the practitioner need not rely upon his or her visual faculties to distinguish between often too subtle differences in those shifts. Thus, the dyes of the present invention and of the prior art are still used as contrast agents, but the differences in the reflective spectra of the stained tissues or cells is measured using an instrument, rather than by eye.

With respect to Applicant's new arguments, although the use of a dye is not exemplified in the prior art's Example 6, as Applicant has noted, the prior art teaches by this example that the inherent spectral properties of the cell's components can enable identification and mapping of retinal abnormalities, such that there is no need to stain the retinal tissue (see Example 6, columns 55-58). However, contrary to Applicant's assertion, the prior art does not teach it is preferable not to use dyes in the methods

described. The prior art teaches that in some circumstances, the inherent spectral properties of the components of the cells can enable differentiation between those components and others, but the prior art teaches in other circumstances staining the cells with dyes, such as methylene blue, is essential, simply because one cannot rely upon the inherent spectral features of the cells or tissue alone to distinguish those cells or tissues from others. Again, staining cells and tissues, such that the varying and contrasting coloration of different cells and tissues enables differentiation of those different cells and tissues, is not a new concept, as evidenced by the prior art of record and further evidenced by Applicant's own disclosure.

It is noted that Applicant has disagreed with the Examiner's interpretation of the prior art's disclosure at column 39, lines 10-16. Applicant has misunderstood the implications of those and the preceding passages of the prior art's disclosure. Again, the teaching is that in some instances, the inherent spectral properties of the components of the cells alone can enable differentiation between those components and others. In other instances, the inherent spectral features alone cannot be relied upon to provide the necessary spectral contrast to enable differentiation.

Further regarding Applicant's assertion the prior art teaches it is preferable not to use a dye, because of the potential toxicity of the dye, other prior art of record indicates non-toxic dyes, such as toluidine blue, are preferably used in methods such as those disclosed by the prior art. This is evident upon review of Applicant's own disclosures at, for example, page 5, lines 19-24, or upon review of the teachings of Tuite et al. (of record). Accordingly, although the prior art suggests the inherent spectral features of cells and tissues can enable one to differentiate those cells and tissues, or components thereof, without need for working with potentially toxic dyes, the ordinarily skilled artisan at the time the of the invention would have appreciated that non-toxic dyes are available, which can be used in those circumstances in which the inherent spectral properties alone are insufficient to provide the necessary spectral contrast, as evidenced by the Tuite et al.

Nevertheless, *arguendo*, if the prior art's disclosures might suggest it is preferable not to stain the cells or tissues, or if the prior art's disclosures might only

suggest to Applicant that the disclosed invention of the prior art be used to identify and/or quantify various cellular structures, as opposed to differentiating cancerous cells from normal cells, it is aptly noted MPEP § 2123 states:

> Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994)

MPEP § 2123 further states:

> A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.").

Therefore, while Applicant has argued the prior art only teaches the use of dyes as contrasting agents to provide contrast between various different cellular structures, as opposed to provide spectral contrast between cancerous and normal cells, the disclosed examples in which the prior art teaches a broader or other use for the therein disclosed invention, which differs from Applicant's claimed invention, does not constitute a teaching away from those embodiments disclosed by the prior art, which are the anticipatory of Applicant's claimed invention.

Despite Applicant's argument the prior art does not teach methods for diagnosing cancer, as stated in previous Office action, the prior art teaches the use of the disclosed invention for differentiation of cancerous cells or tissue in vivo in colon, bladder, lungs, cervix, and other internal organs in Example 7 (column 58). At page 9 of the amendment, Applicant has remarked the prior art's Example 7 is merely prophetic. In reply, the prior art is presumed operable and enabled by the disclosure. MPEP § 2121 states:

> When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption

> of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP § 716.07.

Furthermore, MPEP § 2121.01 states:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention not novel' or anticipated' within section 102, the stated test is whether a reference contains an enabling disclosure'... ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

At page 13 of the amendment, Applicant has asserted the term "*in situ*" is used to refer to freshly excised and otherwise living tissue. This definition of "*in situ*" is unduly narrow, as the term is used in the art to mean simply "in the natural or normal place". Nevertheless, contrary to any assertion that the prior art does not teach a method for *in situ* diagnosis, as the prior art teaches the method can be practiced by endoscopy, for example, it is apparent that the method can be used to diagnose cancer in its natural or normal place, or where it is confined to its natural or normal site of origin.

In reply to Applicant's argument that it is only by the improper use of Applicant's teachings that the Examiner can supply, in hindsight, the deficiencies of the prior art, hindsight cannot have been used, since the instant rejection is under 35 USC § 102 and therefore the prior art is not deficient in teaching all the limitations of the claims that apply to the particular embodiment encompassed by the claims, which is taught by the prior art. Admittedly, the prior art does not teach toliudine blue O, but then that is precisely why the rejection of the claims under 35 USC § 103(a) as being unpatentably obvious in view of Tuite et al. was made.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

> patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1, 5, 7-11, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,784,162-A in view of Tuite et al. (*Journal of Photochemistry and Photobiology B: Biology* 21: 103-124, 1993), as evidenced by Vaezy et al. (*Journal of Microscopy* **163**: 85-94, 1991) and Marchesini et al. (*Photochemistry and Photobiology* **55**: 515-522, 1992) for the reason set forth in section 15 of the previous Office action mailed December 18, 2002.

At page 18 of the amendment filed August 27, 2003, Applicant has traversed this ground of rejection. Applicant has argued the conclusion of obviousness is based on the improper use of hindsight, since Tuite et al. teaches other dyes, apart from toluidine blue O, such that there would be no motivation to select toluidine blue O from the among the others. Furthermore, Applicant has argued, if one were to select toluidine blue O, it would be as a contrast agent. So, Applicant has asserted no teaching or suggestion in any of the combined references of the method recited in the instant claims.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention

where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as stated in the previous Office action, given the teachings of the prior art, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used toluidine blue O in the methods of '162, because both methylene blue and toluidine blue had been characterized as non-toxic and known to selectively stain cancer cells, as evidenced by the prior art of record. While the previous Office action stated, one of ordinary skill in the art at the time the invention was made would have been motivated to use toluidine blue in the methods of '162 to confirm the results of analyses in which methylene blue had been used, Applicant has asserted that the particular selection of toluidine blue O would not have been made. Toluidine blue O and methylene blue have art recognized suitability for the intended use as recited in the claims. See MPEP §§ 2144.06 and 2144.07.

An applicant's expressed recognition of an art-recognized or obvious equivalent may be used to refute an argument that such equivalency does not exist. See *In re Scott*, 323 F.2d 1016, 139 USPQ 297 (CCPA 1963). See MPEP § 2144.06. Therefore, is aptly noted that at page 5, lines 19-24, the specification discloses that toluidine blue O has found more widespread application than methylene blue.

In reply to Applicant's argument that if one were to select toluidine blue O, it would be as a contrast agent, that is precisely correct. Toluidine blue O would be selected because it can be used as a contrast agent. The dye is metachromatic and differentially stains, or facilitates contrasting coloration of cancerous and normal cells or tissues, which contrasting coloration results from differential light absorption and reflection by the stained cells or tissues. Using the prior art's SpectraCube™ to measure and quantify the reflective spectra of the cell or tissues and then comparing those spectra to a library of spectra acquired using known cancerous or normal cells or tissues, the ordinarily skilled artisan would have a reasonable expectation of success in

rendering a diagnosis of cancer since the prior art's methods can be used to differentiate cancerous cells and normal cells.

Conclusion

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
June 4, 2004

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